Chapter 1

Management of Complicated Urinary Tract Infection

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.74556

Abstract

The management of complicated urinary tract infection (UTI) remains a challenge since the coexisted conditions may significantly decrease the successful rate of treatment. In this chapter, the specific conditions including indwelling catheter, urolithiasis, neurogenic bladder, vesicoureteral reflux and pregnancy are listed. In terms of each condition, the potential influence on UTI and management strategy is discussed. Not only is the current evidence reviewed but also we present our experience on management of complicated UTI.

Keywords: urinary tract infection, catheter, urolithiasis, neurogenic bladder, vesicoureteral reflux, pregnancy

1. Introduction

Urinary tract infection (UTI), defined as an inflammatory response of the urothelium induced by a pathogenic organism, is one of the most common infectious diseases. It is estimated that one-third of the women may experience UTI by the age of 24, and half of the women suffer from at least one symptomatic UTI during their lifetime [1]. Basically, UTI can be classified as uncomplicated and complicated infection. The former is normally confined to bladder, which can be treated by short-course antibiotics. The latter refers to an infection associated with a condition which can increase the rate of therapy failures significantly. It is reported that 25–30% of adult women with UTI have at least one risk factor causing complicated UTI [2]. The common conditions which may result in complicated UTI are presented in **Table 1**. Not only do these factors decrease treatments' successful rate but also increase the recurrence risk of UTI. Therefore, when a complicated UTI is treated, management of the conditions needs to be taken into consideration.

Category	Specific conditions
Foreign bodies	Indwelling catheter
	Urolithiasis
Structural or functional abnormality of urinary tract	Neurogenic bladder
	Vesicoureteral reflux
	Obstructive uropathy
Others	Pregnancy
	Diabetes mellitus
	Renal failure
	Immunosuppression after kidney transplantation

Table 1. Specific conditions causing complicated UTI.

2. Catheter-associated UTI

Catheter-associated UTI is one of the most common complicated UTIs. It has been reported that catheter-associated UTI may lengthen the patients' hospital stay and increase the mortality and the direct medical cost [3, 4]. Typically, the microorganisms can enter urinary tract through the extraluminal or intraluminal route. The former means microbial pathogens can invade the bladder through the gap between the catheter and urethra, whereas the latter indicates that causative agents migrate to bladder along the internal lumen of the catheter. According to the data from National Healthcare Safety Network (NHSN), the top three pathogens causing catheter-associated UTI are *Escherichia coli* (21.4%), *Candida spp.* (21.0%) and *Enterococcus spp.* (14.9%), followed by *Pseudomonas aeruginosa* (10.0%), *Klebsiella pneumoniae* (7.7%) and *Enterobacter spp.* (4.1%) [5]. With the duration of catheterization prolonging, the pathogens may induce the formation of biofilm on the surface of the catheter, which causes the occurrence of antibiotic resistance [6]. Traditionally, antimicrobial therapy was considered as a prevention strategy for catheter-associated UTI. However, a survey in two Dutch district hospitals showed that the use of antibiotics was associated with the development of bacteriuria in patients catheterized for 3–14 days [7]. A recent cohort study further revealed that empirical antibiotic treatment had no effect on patients' prognosis [8]. Both European Association of Urology (EAU) and Infectious Diseases Society of America (IDSA) guidelines recommend against the use of systemic antimicrobial prophylaxis for catheter-associated UTI [9, 10]. By contrast, the consistent recommendation identified across guidelines is removal of the catheter as soon as possible. However, some patients have to be catheterized for a long time due to various disorders. For those patients, some practical strategies are developed to prevent and manage the catheter-associated UTI.

2.1. Alternatives to indwelling urethral catheter

Instead of indwelling urethral catheterization, some alternative approaches have been developed to minimize the catheter-associated UTI. Those approaches include use of external

catheter, intermittent catheterization and suprapubic catheterization. Condom catheter is the most common external equipment, which is suitable for patients with severe storage lower urinary tract dysfunction such as urinary incontinence. It has been reported that condom catheter has a significant advantage in comparison with indwelling catheter. A randomized controlled trail (RCT) demonstrated that condom catheter might reduce 80% risks of catheter-associated UTI or death compared to indwelling catheter. Additionally, patients with condom catheter presented a significant higher satisfaction rate than ones with the indwelling catheter [11].

For patients with severe voiding lower urinary tract dysfunction, intermittent or suprapubic catheterization is an option to replace indwelling catheter. An early study investigated the incidence of bacteriuria in patients with intermittent or indwelling catheterization. Based on the results of urine culture, 32% of patients treated with intermittent catheterization had bacteriuria, which is significantly lower than 61% in ones with an indwelling catheter [12]. Another study revealed that patients with intermittent catheterization had less chance to suffer from pyelonephritis than the counterparts with indwelling catheterization (5 vs. 25%, $P < 0.01$) [13]. In a multicentered RCT, 87 patients with a postvoid residual (PVR) bladder volume of more than 150 ml were allocated to receive intermittent or indwelling catheterization. After 3 days, a significant lower risk of developing bacteriuria was found in the intermittent catheterization group compared with the indwelling catheterization group (14 vs. 38%, $P = 0.02$), so was the risk of UTI (12 vs. 33%, $P = 0.03$). In terms of patients' satisfaction, no marked difference was found between these two groups [14].

In general, intermittent catheterization can be practiced by a clean or sterile technique. Originally, sterile intermittent catheterization was applied as a standard method. In 1947, Guttman published the first report about sterile intermittent catheterization. In the report, he showed that this technique could decrease the risk of UTI and might be helpful for patients' recovery of micturition. About 19 years later, Guttman further reported his experience in the use of sterile intermittent catheterization. During 11 years, he applied this technique to manage a total of 476 patients. Based on the data from 409 males, the technique was related to an extremely low incidence in UTI, vesicoureteral reflux, hydronephrosis and urolithiasis. Although sterile intermittent catheterization has some advantages, it is costly and time-consuming. In 1970, Hence Lapides and Betty S. Lowe introduced another technique, that is, clean and intermittent self-catheterization. Subsequently, they published a series of articles in which they showed that this technique could not increase the incidence of UTI. Later, a number of emerged evidence suggested that sterile intermittent catheterization could not provide an extra benefit compared to clean techniques. Two RCTs demonstrated that different technique was associated neither with overgrowth of microorganisms in urinary tract nor with the symptomatic UTI [15, 16].

Suprapubic catheterization provides a treatment option for patients who are not suitable for intermittent catheterization such as those with low compliance bladder. Evidence has illustrated that suprapubic catheter may bring more benefits for patients compared to transurethral catheter. A retrospective cohort study showed that patients with suprapubic catheter had less clinical visits due to pain than ones with indwelling urethral catheter [17]. The result from a meta-analysis revealed that suprapubic catheterization was associated with a significant lower risk of

bacteriuria and less discomfort compared with transurethral catheter [18]. A prospective open-labeled study presented that women with postoperative urinary retention favored suprapubic catheter due to a better catheter-specific quality of life [19]. According to the result from a network meta-analysis, indwelling urethral catheter did not increase the risk of UTI compared with either suprapubic tube or intermittent catheterization when duration of catheter was less than 5 days. In contrast, suprapubic tube or intermittent catheterization was associated with a lower rate of UTI when long-term catheterization is needed [20]. Based on our experience, suprapubic catheter has a significant advantage for male patients. We used suprapubic catheter to manage more than 20 male patients who suffered from recurrent acute bacterial prostatitis or epididymitis secondary to indwelling urethral catheter. We found that no one experienced these genitourinary infections again after the technique of catheterization was changed. Additionally, suprapubic catheter allows patients to observe their recovery of voiding function. We encourage patients to try to urinate with a closed suprapubic catheter if they have a low detrusor leak-point pressure (<40 cmH_20) assessed by urodynamics, which means patients' attempt of voiding cannot bring about upper urinary tract deterioration. After spontaneous voiding, patients need to open the suprapubic catheter and measure the PVR. Once the PVR is low enough, the removal of suprapubic catheter can be taken into consideration.

2.2. Catheter selection

To prevent the catheter-associated UTI, some special catheters have been designed and developed. They mainly include silver-coated, antibiotic-coated, hydrophilic and novel trefoil catheters.

As is known, silver is a kind of antiseptic. So it was hypothesized that catheter coated with silver could reduce the risk of UTI in patients treated by the indwelling catheter. Based on this hypothesis, a variety of silver-coated catheters have been developed. However, the efficacy of these catheters on UTI prevention varies from one to another. Evidence showed that silver alloy-coated catheter might reduce the incidence of UTI, but the silver oxide-coated one would not. A prospective single-center study conducted in Hong Kong investigated the incidence of UTI in patients with a silver alloy and hydrogel-coated catheter, which was compared with the counterparts with a standard catheter. The results showed that the incidence of UTI per 1000 catheter days was 6.4 and 9.4 in the silver-coated catheter group and standard catheter group, respectively. The silver-coated catheter group presented a 31% reduction in risk of UTI [21]. Lederer et al. reported the similar results in a retrospective cohort study in which 7 medical centers with 2778 active acute care beds in the United States were involved. They found that the silver alloy and hydrogel-coated catheter could cause a 47 and 58% relative reduction in UTI rate, respectively, compared to the conventional catheter when a different definition was applied [22]. In contrast, two clinical trials revealed that the use of silver oxide-coated catheter could not reduce the incidence of UTI and bacteriuria in comparison with standard catheter [23, 24]. Besides the two silver-coated catheters mentioned earlier, another silver nanoparticle-fabricated catheter has been developed. According to an experimental study, this silver nanoparticle catheter had significant antimicrobial and antibiofilm properties, as well as a remarkable ability to cause disorganization of bacterial cell membrane, which may prevent UTI effectively [25].

It has been shown that antibiotic-coated catheter has a significant antimicrobial activity. Desai et al. found that nitrofurazone-impregnated catheter could decrease the adherence of pathogenic microorganisms to catheter markedly, but the effect could only persist for 5 days after the catheterization [26]. Regev-Shoshani et al. further reported that both nitrofurazone- and nitric oxide-coated catheters had a great effect on the prevention of microbial growth and biofilm formation, which was more effective than silver-coated catheter [27]. Despite lack of available clinical data so far, the antibiotic-coated catheter may bring potential benefits for patients with indwelling catheter.

Hydrophilic catheter may decrease the friction between catheter and urethra during catheterization. Consequently, it reduces the potential mucosal trauma which can result in the bacterial colonization. A multicentered RCT showed that the use of hydrophilic catheter might decrease approximately one-third the risk of developing symptomatic UTI compared with standard catheter [28]. Similarly, the evidence from a meta-analysis supported marked benefits of hydrophilic catheter in terms of the incidence of UTI [29].

A novel trefoil catheter has been developed. Although it has not been reported for use in clinical practice, the preclinical study has shown its advantages. Sun et al. performed an experiment in which 66 rabbits were catheterized using either conventional or novel trefoil catheter randomly and reported that the novel catheter could decrease the incidence of bacteriuria. In addition, it was also found that the trefoil catheter caused a significant slighter mucosal inflammation than conventional catheter based on endoscopic assessment [30].

2.3. Catheter care

Catheter care is important for patients with an indwelling catheter since appropriate care can decrease the incidence of UTI. Both EAU and IDSA guidelines recommend maintaining a closed drainage system all the time [9, 10]. Once any breaks are detected, both the catheter and collecting system must be replaced as soon as possible. Besides, it is crucial to keep the drainage tubing being below the level of the patient's bladder and above the level of the collection bag, which can avoid the reflux of urine in drainage system. To minimize the risk of UTI, different types of collecting systems were developed. However, current evidence fails to show their different effects on prevention of UTI. Sullivan et al. conducted a RCT, in which 51 hospitalized dogs were catheterized with either an open or closed urine collection system. After analyzing the incidence of bacteriuria, they concluded that the type of urine collection system (open vs. closed) was not associated with the risk of developing bacteriuria [31].

In terms of the time point to change catheter, most guidelines recommend against changing catheter routinely. Instead, it is recommended to change the catheter before blockage occurs. Furthermore, some strategies including bladder irrigation with citric acid solution and oral acetohydroxamic acid have been proven to be effective for prevention of catheter blockage [32, 33]. By contrast, bladder washing with saline is not recommended due to lack of effectiveness [34].

3. Urolithiasis

Urolithiasis is one of the most common urological diseases with a rising incidence around the world. In general, UTI is usually considered as a complication of urolithiasis. Actually, it is also a potential pathogenic factor for a special urinary stone, struvite. Basically, the formation of struvite originates with the bacterial decomposition for urea. Some bacteria, including Proteus and Klebsiella, can decompose urea into ammonia and carbon dioxide, which can be further converted into ammonium and bicarbonate, respectively, and consequently, elevate the pH value of urine. With an alkaline urinary environment, the ammonium has a strong ability to combine with magnesium and phosphate. Once these chemical substances become supersaturated in urine, they will crystallize and deposit the struvite. The existence of urinary stone, especially struvite, may cause UTI difficult to treat because the stone may act as a nidus for microorganisms and result in obstruction in urinary tract.

According to our experience, when UTI and urolithiasis coexist, the individualized management strategy should be taken into consideration. If the stone causes a urinary tract obstruction, the initial treatment should focus on the decompression of the collecting system, which can avoid the infection being exacerbated. Normally, the best way of decompression is to remove the stone as soon as possible, which can be achieved either by ureteroscopic lithotripsy or by percutaneous nephrolithotripsy. However, if the patient cannot tolerate these minimally invasive surgeries, indwelling ureteral stent and percutaneous nephrostomy tube could be the optional treatment. Only with an unobstructed collecting system can the subsequent antibiotic therapy for UTI be efficient. For patients with coexistence of UTI and nonobstructive stone, empiric antibiotic therapy can be the initial treatment. Only when the UTI fails to manage, the invasive intervention is considered to remove the stone.

4. Neurogenic bladder

Neurogenic bladder refers to the bladder dysfunction secondary to a certain disease of the central nervous system or peripheral nerves. The specific conditions causing neurogenic bladder are various and the most common one is spinal cord injury, followed by multiple sclerosis, cerebral vascular events and Parkinson's disease [35]. Moreover, long-standing diabetes plays an important role in the development of neurogenic bladder. It is reported that patients with neurogenic bladder have a significant increased incidence of UTI. An observational study in which 46,000 patients with neurogenic bladder were investigated and followed up showed that 29.2–36.4% of patients were diagnosed with lower UTI annually [35]. Another study revealed that 81% of patients with spinal cord injury experienced at least one UTI during a period of 5 years [36]. The etiology of UTI caused by neurogenic bladder is diverse. It is reported that the bladder ischemia and defect of glycosaminoglycan layer induced by bladder overdistension reduce the barrier function of urothelium [37, 38]. Moreover, immunological impairment of bladder mucosa involving NK cell, B and T cell further decreases the bladder's ability to defend the pathogens [39, 40].

For patients with neurogenic bladder, the clean intermittent self-catheterization is the most common technique to avoid bladder overdistension. It remains a big issue whether prophylactic

antibiotics can prevent bacteriuria and UTI in patients performing clean intermittent self-catheterization due to neurogenic bladder. Two double-blind, placebo-controlled, crossover trials showed that nitrofurantoin prophylaxis could reduce the risk of bacteriuria and UTI significantly [41, 42]. On the contrary, a Cochrane systematic review demonstrated that the evidence failed to prove the certain benefits of antibiotic prophylaxis in patients with clean intermittent self-catheterization [43]. In a recently published case series study, Cox L et al. described a successful treatment in reduction of UTI in patients with clean intermittent self-catheterization using intravesical instillations of gentamicin [44]. However, the treatment strategy needs to be further verified by well-designed RCTs.

5. Vesicoureteral reflux

Vesicoureteral reflux is the most common risk factor for UTI in children. It is reported that 30–40% of children with their first UTI episode are affected by this disorder [45, 46]. In general, vesicoureteral reflux is graded from I to V (mild to severe) according to the height of reflux up the ureter and degree of dilatation of the ureter. A high grade of vesicoureteral reflux, defined as grade IV and V, may lead to the renal scars due to UTI, which may further cause renal failure. Conventionally, antibiotic prophylaxis has been considered as the standard management for patients with vesicoureteral reflux. However, a large cohort study revealed that continuous antibiotic prophylaxis could not decrease the risk of recurrent UTI but might increase the risk of bacteria resistant to the antibiotic in children with vesicoureteral reflux [47]. As an approach to eliminate reflux, some invasive interventions including anti-reflux surgery and injection of bulking agent are used to reduce the breakthrough UTI. Basically, the surgical options include open or laparoscopic ureteral reimplantation. Based on clinical assessment, the reported successful rate for open and laparoscopic approach is 80–95% and 90–93%, respectively [48–50]. In contrast, the endoscopic injection presents a lower treatment successful rate in the range of 50–93% [48]. From our experience, surgical intervention may be an effective therapy for the patients who still suffer from UTI even on continuous antibiotic prophylaxis.

6. Pregnancy

It is reported that pregnant women have an increasing risk of UTI, especially upper UTI, because the physiological changes induced by pregnancy make them more likely to suffer from pyelonephritis. On the one hand, elevated level of progesterone during pregnancy can induce the relaxation of ureteric smooth muscles, which may lead to the urine retention in the renal collecting system and ureter. On the other hand, the noticeable increase in renal blood volume and glomerular filtration rate may contribute to the renal pelvic and ureteral dilation. The dilated upper urinary tract provides pathogens with a permissive environment to grow and reproduce. As a result, bacteriuria will develop pyelonephritis in 25–40% of pregnant women. The independent risk factors include history of UTI, low socioeconomic status, indigence, intercurrent diabetes and sickle cell trait. Therefore, short-course antibiotic therapy should be applied to prevent developing ascending UTI, once the bacteriuria is identified in pregnant

women. It is investigated that the antibiotic therapy can reduce the incidence of pyelonephritis by 75% [51]. Generally, a three-day course of antibiotic therapy directed by urine culture is recommended for both symptomatic lower UTI and asymptomatic bacteriuria. When the result of culture is not available, an empiric therapy with a ß-lactam or nitrofurantoin can be used as the initial treatment. For patients with upper UTI, a 14- to 21-day course of intravenous antibiotic therapy should be adopted. The reported effective antibiotic includes a third-generation cephalosporin, gentamicin or aztreonam, which can be used as the initial treatment before the result of culture is available. In addition, it is crucial to identify whether an obstruction exists in every pregnant woman. Once the obstruction is diagnosed, it can be relieved by ureteral stent or percutaneous nephrostomy tube. For patients with ureteral stent or percutaneous nephrostomy tube, it is necessary to use the antibiotic continuously until after delivery.

7. Conclusion

The treatment of complicated UTI remains a challenge because the coexisted conditions are diverse. Appropriate management for these conditions is the prerequisite achieving a successful treatment for complicated UTI.

Acknowledgements

This work was supported by Beijing Municipal Science & Technology Commission No. Z161100000516156 and grant 2014S292 from Guang An Men Hospital, China Academy of Chinese Medical Sciences.

Conflict of interest

None.

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